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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/165 // A61K 9/06

A1

(11) International Publication Number: WO 93/17674

(43) International Publication Date: 16 September 1993 (16.09.93)

(21) International Application Number: PCT/SE93/00208

(22) International Filing Date: 10 March 1993 (10.03.93)

(30) Priority data:
9200762.4 12 March 1992 (12.03.92) SE

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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: TOPICAL USE OF LOCAL ANAESTHETIC AGENTS FOR RHEUMATOID ARTHRITIS AS WELL AS A PHARMACEUTICAL PREPARATION AND A METHOD FOR THE TREATMENT THEREOF

(57) Abstract

Use of one or more local anaesthetic agents, especially lidocaine and prilocaine, for the manufacture of a topical pharmaceutical preparation with curing effect on rheumatoid arthritis.

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Topical use of local anaesthetic agents for rheumatoid arthritis as well as a pharmaceutical preparation and a method for the treatment thereof

Field of the invention.

The present invention is related to the use of a formulation intended for topical application, and containing one or more local anaesthetic agents, or pharmaceutically acceptable salts thereof, for the treatment of rheumatoid arthritis and related inflammatory conditions.

Background of the invention.

Rheumatoid arthritis is a disease with a largely unknown etiology. In most cases it is a chronic disease often leading to pain and disability, especially in later stages of the disease. Rheumatoid arthritis (RA) is considered to be an inflammatory condition with symmetrical engagement of the joints and tendon sheets. Widenfalk B. has found several indications suggesting RA to be mediated to a partial extent via the nervous system.

Widenfalk B., "A spinal transcommisural connection for symmetrical reflex response, Scand. J, Plast Reconstr. Hand. Surg. 24: pp. 207-212, (1990), and "Sympathetic , innervation of normal and rheumatoid synergical tissue, Scand. J, Plast Reconstr. Hand. Surg. 25: pp. 31-31, (1991), Widenfalk B. et al "Origin of Sympathetic and sensory innervation of the Elbow Joint in the Rat: A Retrograde Axonal Tracing study with Wheat Germ Agglutinin conjugated Horse-Radish Peroxidase., The J. of Comparative Neurology 271: pp. 313-318 (1988) and Widenfalk B., Wiberg M. "Origin of sympathetic and sensory innervation of the knee joint, Anat. Embryol. 180: pp. 317-323, (1989). An indication that RA is mediated this way is the finding that a patient who suffers from the disease, and also sustains a cerebrovascular

lesion with half-sided paresis does not show any inflammatory process in the paretic part of the body where the nerve transmission is damaged. Injection of anti-inflammatory agents, e.g. steroids into the joints of patients with RA have proven their therapeutic value by the treatment of the disease, and is considered to be the treatment of choice for such conditions. Injections into the joints is a painful clinical procedure, and in the case of RA affecting several sites, e.g. in the hands, many injections are often necessary. In order to minimize the pain by these procedures, a local anaesthetic is frequently added to the steroid to decrease or eliminate the pain caused by the local irritating effect of the steroid containing solution. The effect of the local anaesthetic added to the solution is entirely aimed at blocking the pain on injection. Local anaesthetics have been found to influence the mediation of an inflammatory tissue response, as described in many publications.

The mechanism of action for the anti-inflammatory effects of local anaesthetics is largely unknown, but has been defined as the result of a combination of a blocking of neural impulse transmission and an effect upon the local inflammatory mediators. A significant protective effect of local anaesthetics, applied prior to a standardized experimental trauma was investigated by Ohlsen L. et al, "Local anaesthetics modifying the dermal response of irridiation. "Acta Oncologica 26 (1987), Fasc. 6, pp. 467-476.

In an experimental study in rabbits the authors found that the pronounced inflammatory response in the dermal tissues of the animals, induced by high-energy irridiation, could be significantly modified, or even completely inhibited, by the topical application of a local anaesthetic (Emla cream), applied to the skin of the experimental animals before or after the tissue-damaging irradiation. The results from this study

indicate that it is possible after topical administration to ensure adequate tissue concentrations of the local anaesthetic for reducing the inflammatory response also in the deeper layers under the topically applied formulation.

Outline of the invention.

It was therefore of interest to investigate if a topically applied local anaesthetic might have a beneficial effect also in cases of RA by reducing the inflammatory process in the joints situated at a distance from the medicated skin areas on the hands of patients with RA. In a patient with prodromal symptoms of RA, including pain and a reduced mobility in both hands, a local anaesthetic formulation (Emla cream) was applied to the joints and adjacent skin areas. The topical anaesthetic was applied under occlusive dressings and left in contact with the skin for 2 hours. This treatment was repeated twice a day, for 2 days. After this treatment the pain had completely receded and the mobility in the treated hand was restored to normal. The duration of the amelioration after this treatment was more than one week, indicating that the duration of the positive effect had no direct relation to the local anaesthetic effect, as such an effect has only a duration of about 5 hours, if investigated with the pin-prick technique, Juhlin L. & Evers H.
EMLA: A New Topical Anaesthetic, Adv Dermatol 5: 75-92 (1990). The positive effect induced by the local anaesthetic in this patient is thus probably related to a temporary break in the viscious-circle type reaction otherwise induced by the inflammatory disease (RA).

In order to further substantiate the beneficial effects in connection with the topical treatment of patients with RA with application of local anaesthetic compositions, five patients with diagnosed rheumatoid athritis in their hands were treated.

Experimental data.

Five patients with diagnosed active rheumatoid arthritis were treated locally with topical treatment of EMLA for two weeks. All five patients noted a positive effect of the treatment with reduced pain and loss of swelling of the affected joints. Improvement of joint motion was also noted objectively and subjectively. In all patients the effect lasted more than two weeks of treatment but only in one patient the swelling was completely gone also six months after treatment.

Pharmaceutical preparations preferred according to the invention.

The topical local anaesthetic formulation used according to the invention is characterized by its ability to penetrate intact skin due to its pharmaceutical properties, or may be transported into the skin and underlying tissues by the use of iontophoresis, or by the addition of a penetration enhancing formulation (e.g. DMSO, DMA or Azone ®).

It should contain at least one local anaesthetic agent in the form of its base or a pharmaceutically acceptable salt therof, or a eutectic mixture of local anaesthetics of the aminoamide type (e.g. lidocaine, prilocaine, bupivacaine, ropivacaine etc.).

The local anaesthetic(s) is(are) incorporated into a jelly, an emulsion, a cream, an ointment, spray solution or a film-forming formulation.

It is also possible to incorporate the local anaesthetic(s) into a pharmaceutical composition with sustained release of the active compound(s). Hereby an even concentration of the active compound(s) during an extended period of time may be achieved without the need for a frequent change of dressings.

A further way to apply the local anaesthetic preparation

is to use sterile, or non-sterile dressings soaked with the local anaesthetic preparation.

The local anaesthetic composition contains between 0.25% - 20% by weight of the local anaesthetic(s), preferably 5% - 10%.

Pharmaceutical preparations

Example 1

Jelly 1 %

Lidocaine hydrochloride monohydrate		10.8 kg
Hydroxypropyl methylcellulose 4000 cps		24,5 kg
Sodium hydroxide 2M to pH 6.3-6.7		
Water for injection	qs ad	1000 l

Lidocaine hydrochloride monohydrate and hydroxypropyl methylcellulose are dissolved in water for injection. The pH is adjusted to 6.3-6.7 with sodium hydroxide and the volume to 1000 l with water.

Example 2

Jelly 2 %

Lidocaine hydrochloride monohydrate		8.65 kg
Hydroxypropyl methylcellulose 4000 cps		9.8 kg
Sodium hydroxide 2M to pH 6.2-6.6		
Water for injection	qs ad	400 l

Lidocaine hydrochloride monohydrate and hydroxypropyl methylcellulose are dissolved in water for injection. The pH is adjusted to 6.2-6.6 with sodium hydroxide and the

volume to 400 l with water. The resulting solution is autoclaved.

Example 3

Solution 40 mg/ml

Lidocaine hydrochloride monohydrate		4.28 kg
Sodium hydroxide 2M to pH 6.5-6.7		≈ 0.46 kg
Purified water	qs ad	95.56 kg

Lidocaine is dissolved in the water. Sodium hydroxide is added to pH 6.5-6.7. The resulting solution is autoclaved.

Example 4

Emulsion cream

Lidocaine	10	g
Miglyol® 812	27.6	"
Arlatone® 289	9.0	"
Carbopol® 934	1.0	"
Water	ad 100	"

The emulsion is prepared by dissolving lidocaine in the oil (Miglyol® 812), whereafter it is melted together with the emulsifier (Arlatone® 289). A minor amount of water is then added to the hot mixture. The resulting mixture is cooled whereafter the thickening agent (Carbopol®) mixed with the rest of the water is added as gel. The resulting mixture is homogenized to such an extent that the substantial part of the oil droplets have a diameter of <3µ. Miglyol® 812 is a hardened coco-fat with mean chain length. Arlatone® 289 is a polyoxy-ethylene fatty acid ester and Carbopol® 934 is a vinyl polymer with active carboxyl groups.

Example 5

Lidocaine		5	g
Miglyol® 812		13.8	"
Arlatone® 289		4.5	"
Carbopol® 934		1.0	"
Water	ad	100	"

An emulsion cream is prepared as described in example 3.

Example 6

Lidocaine		2.5	g
Miglyol® 812		6.9	"
Arltone® 289		2.25	"
Carbopol® 934		1.0	"
Water	ad	100	"

An emulsion cream is prepared as described in example 3.

Example 7

Prilocaine, base	52	g
Lidocaine	48	g

The two local anaesthetically active compounds in crystalline form are weighed together and heated to 30°C, whereby the two compounds melt and form a homogenous oil. The mixture of crystals have a melting point of 22°C. The mixture is then applied onto a carrier of paper in an amount of 1.5 mg/cm². At use the carrier in suitable size is applied on the affected joints. The best mode of carrying out the invention known at present is to use the preparation according to Example 7.

Conclusions

According to the present invention it has thus surprisingly been found that patients with rheumatoid

arthritis have been successfully treated, with regard to pain and manual disability, with the exclusive use of topical application of a composition containing local anaesthetics. The follow-up period of these patients has been up to six months, after termination of the local application of the local anaesthetic.

Claims

1. Use of one or more local anaesthetic agents or pharmaceutically acceptable salts therof in the manufacture of a topical pharmaceutical preparation without preservatives with curing effect on rheumatoid arthritis.

2. Use according to claim 1, wherein the preparation is used for its healing effect on rheumatoid arthritis on the hands.

3. Use according to claim 1, wherein the local anaesthetic is an eutectic mixture of lidocaine and prilocaine.

4. Use according to claim 1, wherein the local anaesthetic agent is lidocaine.

5. Use according to claim 3, wherein lidocaine and prilocaine are in the form of their bases.

6. Use according to claim 4, wherein lidocaine is in the form of its hydrochloride.

7. A method for the treatment of rheumatoid arthritis comprising topical administering to a patient suffering therefrom an amount of one or more local anaesthetic agents or pharmaceutically acceptable salts thereof sufficient for the treatment of said disease.

8. A pharmaceutical preparation for the use in the topical treatment of rheumatoid arthritis wherein the active ingredient is one or more local anaesthetic agents or pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00208

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/165 // A 61 K 9/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, MEDLINE, EMBASE, CLAIMS, CHEMICAL ABSTRACTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4628052 (RAYMOND F. PEAT), 9 December 1986 (09.12.86)	1-2,8
Y	--	3-6
Y	WO, A1, 8911853 (AKTIEBOLAGET ASTRA), 14 December 1989 (14.12.89)	3-6
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
21 June 1993	23 -06- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00208

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (see PCT Rule 39(iv).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/05/93

International application No.
PCT/SE 93/00208

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4628052	09/12/86	NONE	
WO-A1- 8911853	14/12/89	AU-A- 3764689	05/01/90